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PROPHYLACTIC AND TREATMENT DRUGS FOR ORGANOPHOSPHORUS POISONING

ANNUAL REPORT

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Fort Detrick, Frederick, Maryland 21701-5012

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ASH STEVENS INC.
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The program is directed at the design and synthesis of candidate treatment or prophylactic drugs as potential defenses against organophosphorus poisoning. During the past year, nine compounds were submitted: four organophosphinates, one organophosphonate, one quaternary pyridine, one tropane ester, one (new) physostigmine analoge, and 5-nonanone oxime.

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SUMMARY

The purpose of the contract is to maintain and operate a synthesis laboratory to provide chemical compounds needed in the development programs of the U.S. Army Medical Research Institute of Chemical Defense (ICD) Edgewood Area, Aberdeen Proving Ground, Maryland.

All compounds were assigned and prioritized by the Contracting Officer's Representative (COR). Nine assignments were completed in the past year as listed below.

	Compound	Code No.	Wt.,g	Date Shipped
1.	4-Nitrophenyl 2-furyl (methyl) phosphinate	CP-02-205	31.0	10/1/89
2.	3-Hydroxy-1-methylpyridinium bromide	CP-02-211	12.0	9/7/86
3.	4-Nitrophenyl dimethyl-phosphinate	CP-02-240	21.0	11/25/86
4.	4-Nitrophenyl chloromethyl (2-methoxyphenyl)phosphinate	CP-03-15	10.0	2/03/87
5.	3-Nitrophenyl 2-propyl chloromethylphosphonate	CP-03-73	10.0 5.0	4/13/87 (to WRAIR)
6.	(3R,6R)-3,6-Dihydroxytropane 3-(S)(-)-tropate hydrobromide	CT-1-73-3	34.0	4/15/87
7.	4-Nitrophenyl dibutyl-phosphinate	CP-03-96-1	8.0	5/12/87
8.	1,2,3,3a,8,8a-Hexahydro-1,3a,8-trimethylpyrollo-[2,3-b]indol-5-o1 (7-carboxy)-heptanoate ester	JD-03-66	1.0	5/12/87
9.	5-Nonanone oxime	CP-03-97	5.0	5/18/87

The compounds were prepared using synthesis techniques used over the past 10 years in work in this area.

FOREWORD

Citations of commercial organizations and trade names in this report do not constitute an official Department of the Army endorsement or approval of the products or services of these organizations.

Acknowledgment

The timely advice and assistance of Dr. Brennie Hackley, Jr., the Contracting Officers Technical Representative (COTR), and Mr. Claire Lieske of the ICD are gratefully acknowledged.

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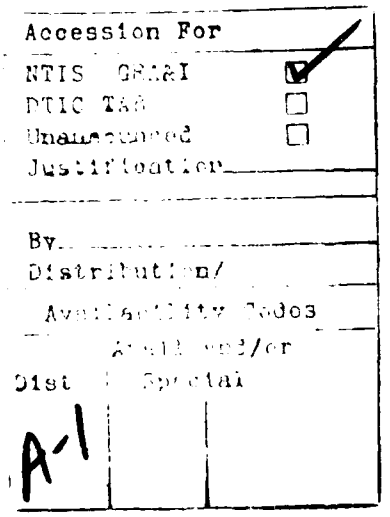


1. INTRODUCTION

The work reported herein represents a continuation of work performed since 1977 under a series of continuing contracts. The primary thrust over the years has been directed at the synthesis of prophylactic and treatment compounds for defense against nerve gas agents (GB,GD,VX). All of the work assignments on these preparative programs were and are made by the Contracting Officers Representative (COR). In addition to candidate prophylactics and treatment against organophosphorus poisoning, the assignments have included intermediates and research compounds required by Army scientist for their inhouse research programs directed at various aspects of OP poisoning.

Historically, starting October 1, 1977, work under the first two contracts (1,2) through January 27, 1981 was directed exclusively to the preparation of organophosphinate esters, 29 in all, as candidate prophylactics. The work was based on a concept delineated by C.N. Lieske and co-workers at the (then) Biomedical Laboratory at Edgewood. Additional support in this early work was provided by the contractor in the form of kinetic studies to measure solvolysis half-lives at two pH levels.

In a third contract (3) this work was continued and expanded to include the synthesis of compounds targeted at other aspects of the problem. This work covered the period September 1, 1981 to September 30, 1984 wherein a total of 48 compounds were prepared plus 10 repeat assignments as well as 25 compounds, 5 g each, shipped to WRAIR. These 48 compounds included the following prophylactics: 25 organophosphinates (including one cyclic phosphinate), a phosphinothioate, 3-nitrophenyl isopropyl methylphosphonate, and seven organocarbamates (including two ferrocenyl analogues). The other assignments (14) involved a variety of research compounds including two sugar oximes as AChE reactivators, one INCAP, a cyclohexyl-piperidine, ν-methyladenosine 5'-triphosphate, 2-aminoethylselenic and 2-aminoethylselenonic acids, monomethyl phosphate (purification), 2,3-dimethyl-3-hydroxybutylamine, pinacolyl dimethylphosphinate and four compounds for the School of Public Health, University of Michigan: three congeneric di-n-butyl 2,2'-dichlorovinyl phosphorus esters and an organic ester.

Under the fourth and current contract starting October 1, 1984, the effort to improve our OP defensive capability in both the propylactic and treatment area was continued. Thus in the first two years of the program (4,5), 41 assignments were completed: 16 organophosphinates, 13 phosphorinanes (cyclic phosphates), two phosphorothioates, four carbamates, three AChE reactivators and three miscellaneous structures: suberyldicholine, a modified (new) tropate ester and a tetraalkylquaternary iodide. In this, the third year of the program, which forms the subject matter of this report, nine

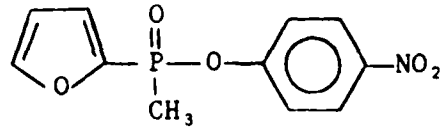
assignments were completed: four organophophinates, one organophosphonate, one tropate ester, one (new) physostigmine analogue and 5-nonanone oxime. A number of assigned compounds represent repeats (see reference 3 for example) which are requested by an Army or another contract investigator via the COR. While we do direct our attention to yield improvements in these cases, the primary goal is to deliver the compound as expeditiously as possible.

Overall, three papers joint with Edgewood personnel have been published (1982, 1984 and 1986) in the prophylactic area, and several meeting papers have been presented by Edgewood personnel which include our supporting contributions. To date, a total of 16 papers (and five patents) have been published in the CW defensive area, most of which relate to various facets of the reactivation of O.P.-poisoned AChE (oximes, total six) as well as research programs relating to the reactivation of "aged" poisoned enzyme (total, six).

2. DISCUSSION OF WORK COMPLETED

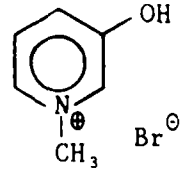
The nine assignments completed in the past year are discussed below.

2.1 4-Nitrophenyl 2-furyl(methyl)phosphinate



The title compound was prepared earlier by Ash Stevens Inc. under a prior contract (3). For the current resynthesis the same synthesis sequence shown in Chart No. 1 was used. 2-Furyllithium, prepared *in situ* from furan and n-butyllithium, was treated with phosphorus trichloride to give tris(2-furyl)phosphine (1) in 70% yield. Treatment of compound 1 with methyl iodide gave the quaternary phosphonium iodide 2 (97%). Treatment of compound 2 with sodium hydroxide in aqueous ethanol at room temperature gave phosphine oxide 3 (66%). Compound 3 was then treated with aqueous hydroxide (1 N) at reflux to give phosphinic acid 4 (58%). Esterification of acid 4 with 4-nitrophenol in the presence of dicyclohexylcarbodiimide gave the title target ester 5 in 53% yield. Yields were somewhat lower in four of the five steps due primarily to a newly hired B.S. chemist. The overall yield was 14% vs 22.5% in the prior work (3).

2.2 3-Hydroxy-1-methylpyridinium bromide



The title compound was prepared by a literature procedure (6) shown below. 3-Hydroxypyridine was treated with methyl bromide in acetone to give the title compound in 64% yield after recrystallization.

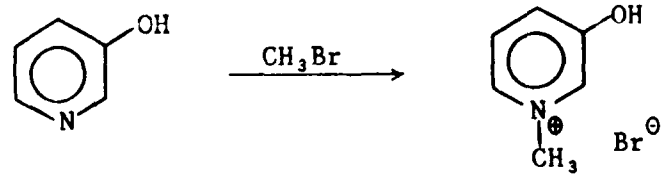
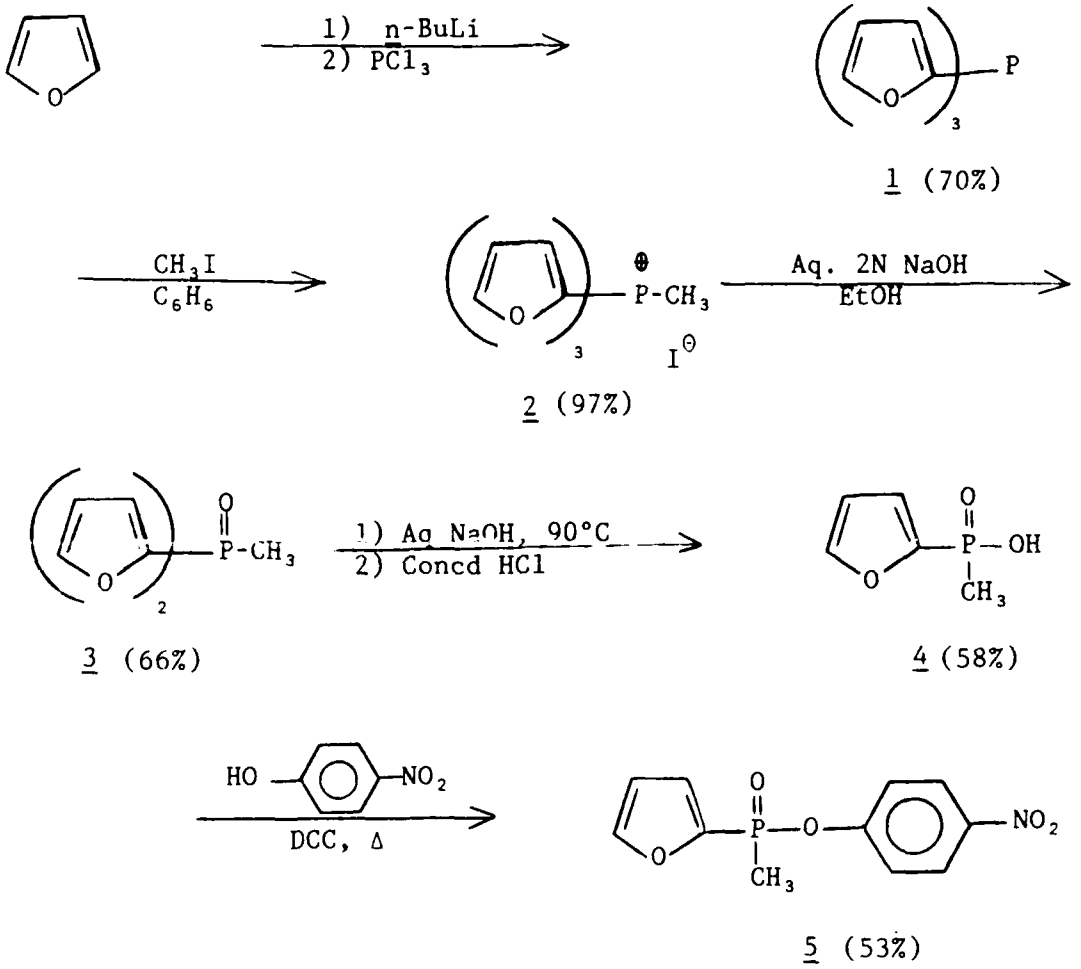
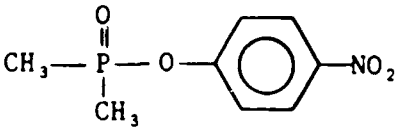


CHART NO. 1

4-NITROPHENYL 2-FURYL(METHYL)PHOSPHINATE

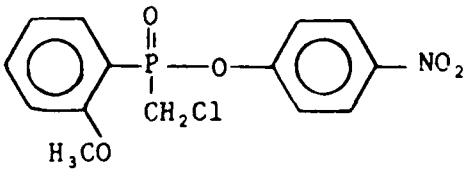


2.3 4-Nitrophenyl dimethylphosphinate



The title compound was prepared earlier by Ash Stevens Inc. under a prior contract (3). For the current resynthesis, the same synthesis sequence shown in Chart No. 2 was used. Tetramethylbiphosphinic disulfide was oxidized with hydrogen peroxide to give dimethylphosphinic acid (1, 81%), which was coupled directly with 4-nitrophenol and dicyclohexylcarbodiimide and gave the title target ester 2 in 33% yield. The yield in the first step was comparable to that obtained previously (3) in the second step, it was 10% lower (3).

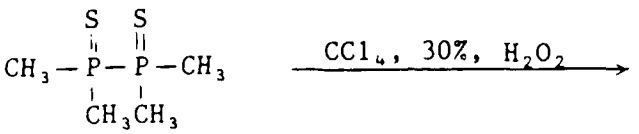
2.4 4-Nitrophenyl chloromethyl(2-methoxyphenyl)phosphinate



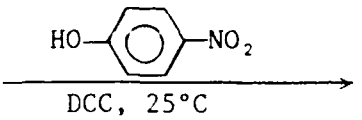
The title compound was prepared earlier by Ash Stevens Inc. under a prior contract (3). The current resynthesis utilized the same synthesis sequence shown in Chart No. 3. Phosphorus trichloride was treated with diethylamine to give intermediate 1 in 81% yield. Treatment of intermediate 1 with 2-methoxyphenylmagnesium bromide gave the phosphonous diamide 2 in 64% yield. Conversion of the phosphonous diamide 2 to the required phosphonous dichloride 3 was accomplished with anhydrous hydrogen chloride in ether in 74% yield. Treatment of intermediate 3 with 1.5 equivalents of paraformaldehyde gave chloromethylphosphinic chloride 4 (52%); this was esterified with 4-nitrophenol in the presence of diisopropylethylamine to give the title compound 5 in 17% yield. Product yields for the first four steps were comparable or slightly higher to those reported previously (3). Yield in the last step was considerably lower. This may be due to partial hydrolysis of the product during workup.

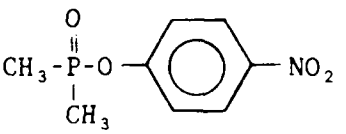
CHART NO. 2

4-NITROPHENYL DIMETHYLPHOSPHINATE



1 (81%)

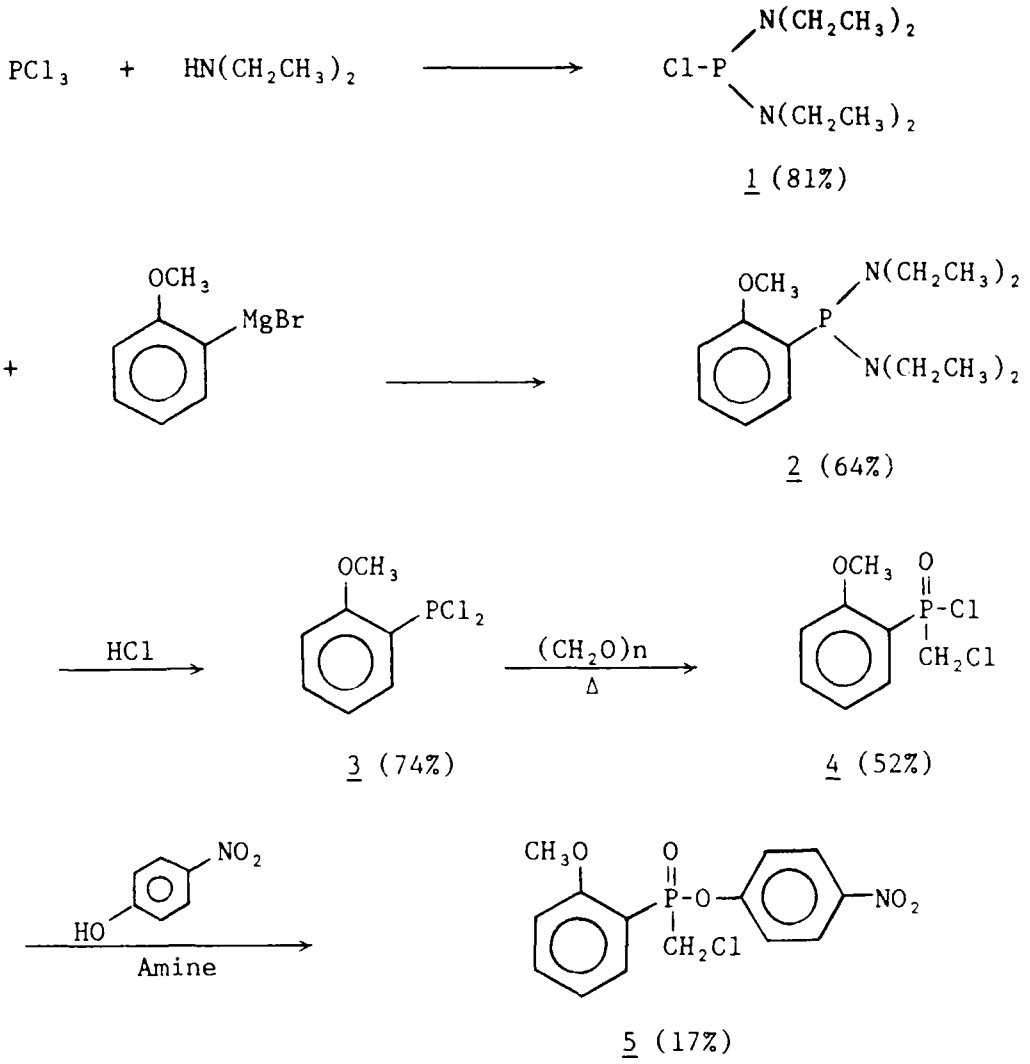




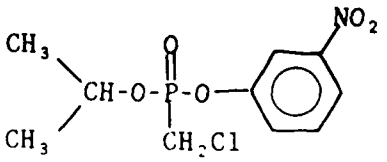
2 (33%)

CHART NO. 3

4-NITROPHENYL CHLOROMETHYL(2-METHOXYPHENYL)PHOSPHINATE



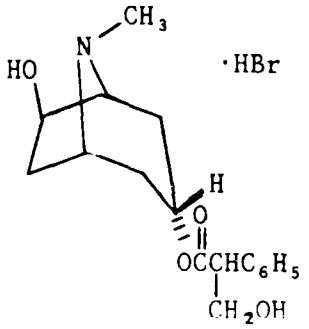
2.5 3-Nitrophenyl 2-propyl chloromethylphosphonate



The title diester of chloromethylphosphonic acid has not been reported in the chemical literature. The synthetic route, shown in Chart No. 4, is similar to that used in these laboratories to prepare analogous mixed diesters of methylphosphonic acid.

Thus, chloromethylphosphonic dichloride was treated with m-nitrophenol and triethylamine in tetrahydrofuran as solvent to give the bis(m-nitrophenyl) ester 1 (85%). Compound 1 was treated with cold, dilute base to give chloromethylphosphonic acid monoester 2 (50%). Finally, esterification of acid 2 with isopropanol and dicyclohexylcarbodiimide gave the title mixed diester 3 (47%).

2.6 (3R,6R)-3,6-Dihydroxytropane 3-(S)(-)-tropate hydrobromide

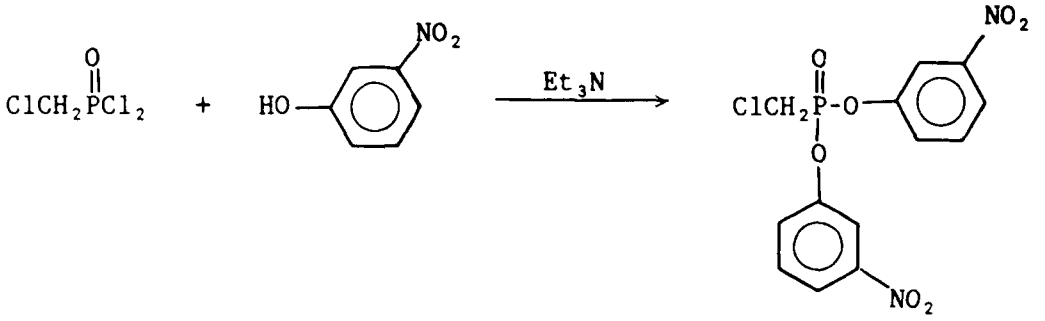


A 13.8-g sample of the title compound was prepared earlier under this contract (5) using a literature procedure (7) shown in Chart No. 5. This same procedure was used for the current resynthesis.

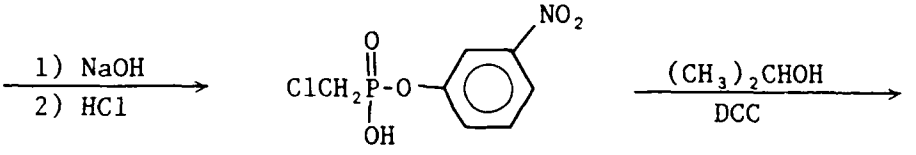
Hydrogenation of scopolamine hydrobromide over neutral Raney nickel catalyst at atmospheric pressure gave a mixture of (3R,6R) and (3S,6S)-3,6-dihydroxytropanes. This mixture of hydrobromide salts was converted to the corresponding free bases (1 and 2) with dilute sodium hydroxide. Treatment with dibenzoyl-L-tartaric acid gave the tartrates which were separated by fractional crystallization from absolute ethanol to give optically pure (3R,6R) isomer 3. Conversion of intermediate 3 to the title hydrobromide salt was accomplished by passage through an ion exchange resin column. The overall yield was almost identical to that obtained earlier (5).

CHART NO. 4

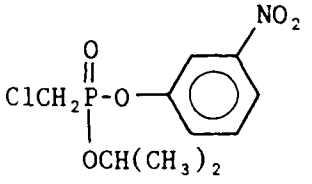
3-NITROPHENYL 2-PROPYL CHLOROMETHYLPHOSPHONATE



1 (85%)



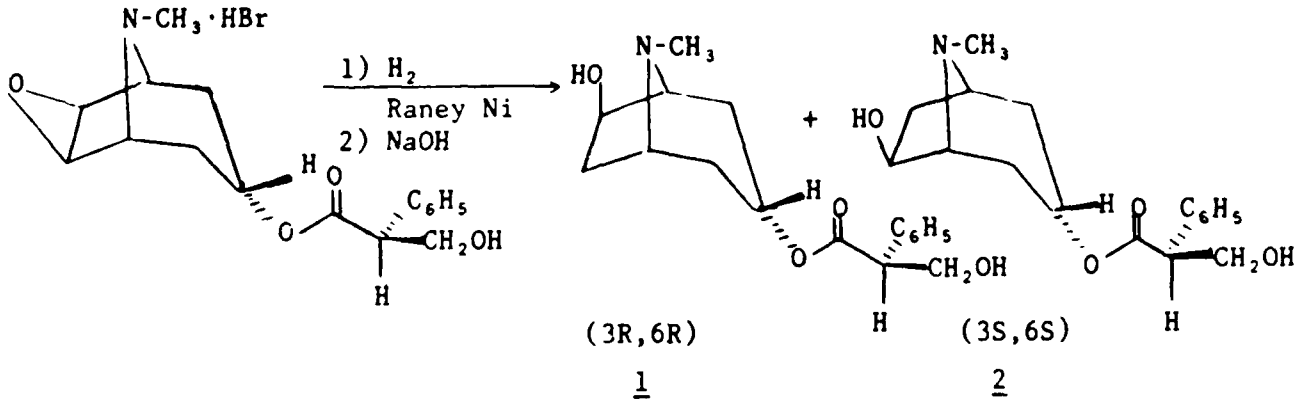
2 (50%)



3 (47%)

CHART NO. 5

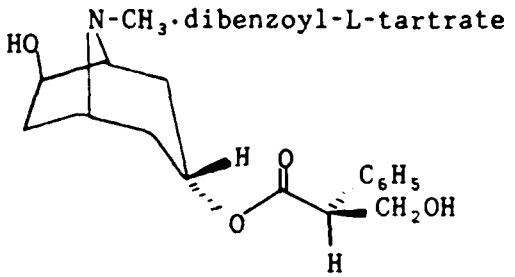
(3R,6R)-3,6-DIHYDROXYTROPANE 3-(S)(-)-TROPATE HYDROBROMIDE



(3R,6R) (3S,6S)

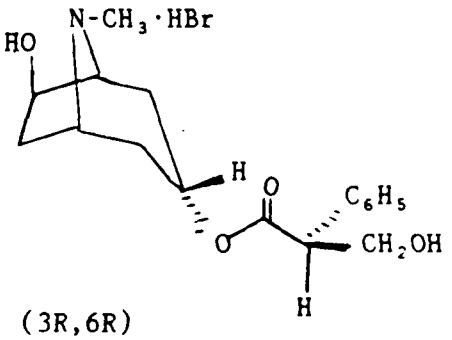
1 2

1) dibenzoyl L-tartaric acid
2) Resolution



3 $[\alpha]_D$ -47.2° (c = 1, CH_3OH)

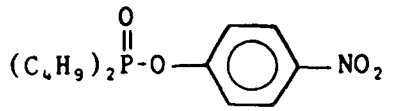
Dowex 2-X8
Br^- form



(3R,6R)

1 $[\alpha]_D$ -10.3° (c = 1, H_2O)

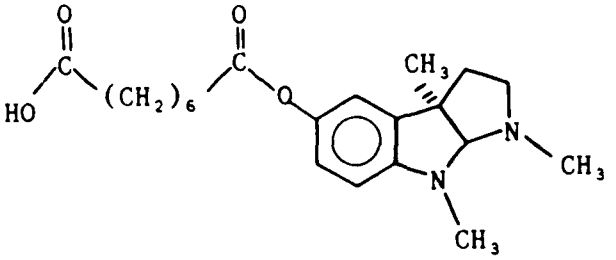
2.7 4-Nitrophenyl dibutylphosphinate



A sample of the title compound was prepared earlier by Ash Stevens Inc. under a prior contract (3). The same sequence shown in Chart No. 6 was used for the current resynthesis.

Diethyl phosphite was treated with three equivalents of n-butylmagnesium bromide and the product was oxidized with bromine according to a literature procedure (8) to give dibutylphosphinic acid (1). The acid 1 was converted to phosphinic chloride 2 by treatment with phosphorus pentachloride. Chloride 2 was allowed to react with 4-nitrophenol and triethylamine to give the title compound 3 which was purified by column chromatography over acidic alumina. Product yields were better than those reported previously (3). The reason for this was not investigated.

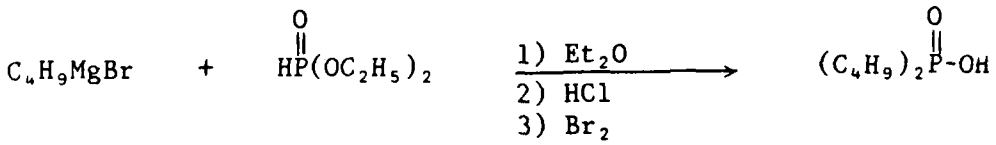
2.8 1,2,3,3a,8,8a-Hexahydro-1,3a,8-trimethylpyrollo[2,3-b]indol-5-ol (7-carboxy)heptanoate ester



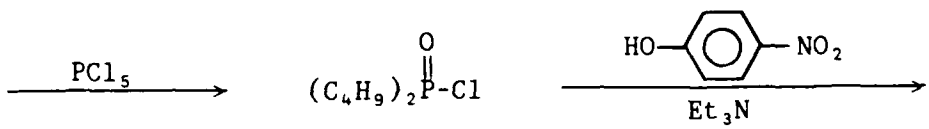
The title ester, a physostigmine analogue, is a new structure not previously reported in the chemical literature. The synthesis route, starting with physostigmine, is shown in Chart No. 7. Thus, physostigmine was hydrolyzed with concentrated hydrochloric acid and the product was treated with bicarbonate to give the substituted indole 1 (eseroline). Treatment of compound 1 with suberoyl chloride did not give the desired 5-O-ester but led instead to N-acylation of the outside ring nitrogen with concomitant ring opening and formation of a nitrogen-to-carbon double bond in the five-membered indole ring. The coupling of compound 1 with monobenzyl suberate in the presence of dicyclohexylcarbodiimide did proceed satisfactorily, however, to give ester 2. Finally, hydrogenolysis of the benzyl group with palladium and 1,4-cyclohexadiene gave the desired title target structure 3.

CHART NO. 6

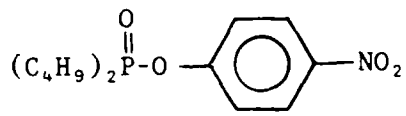
4-NITROPHENYL DIBUTYLPHOSPHINATE



1 (65%)



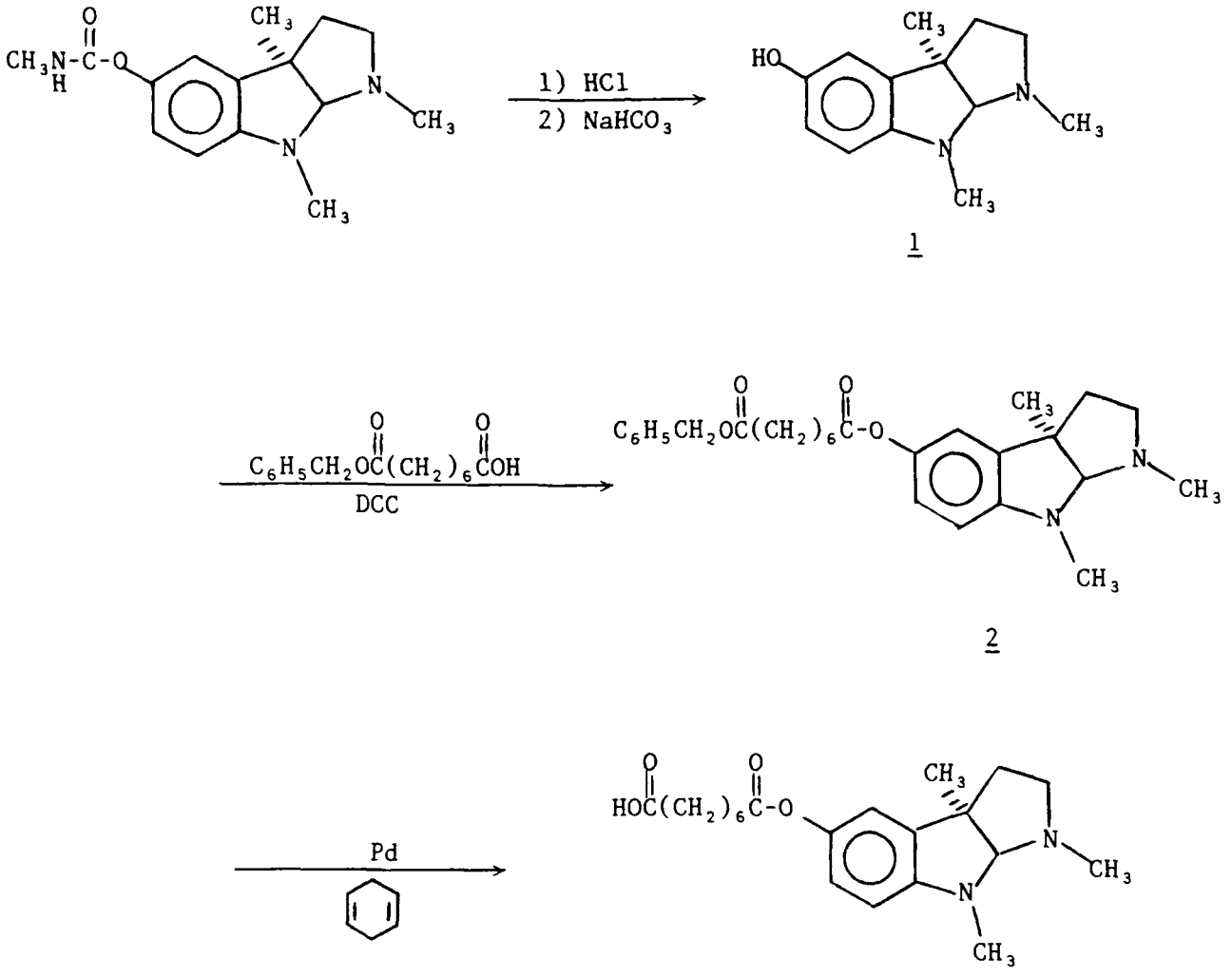
2 (93%)



3 (65%)

CHART NO. 7

1,2,3,3a,8,8a-HEXAHYDRO-1,3a,8-TRIMETHYLPYROLLO-[2,3-b]INDOL-5-OL (7-CARBOXY)HEPTANOATE ESTER



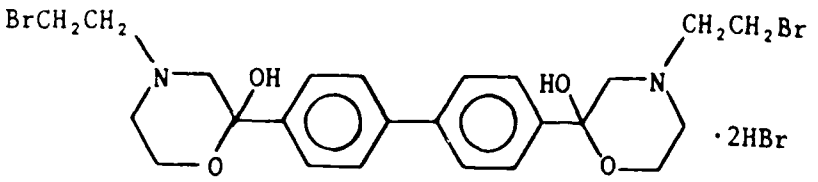
2.9 5-Nonanone oxime

$$CH_3(CH_2)_3\overset{\overset{NOH}{\|}}{C}(CH_2)_3CH_3$$

The title compound was prepared by the reaction of 5-nonanone with hydroxylamine in aqueous ethanol. The crude product was purified by distillation to give the pure oxime (70%), a mobile oil.

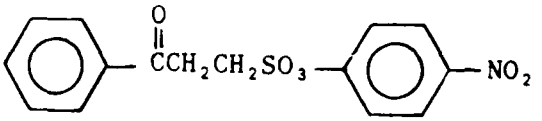
3. WORK IN PROGRESS

3.1 2,2'-(4,4'-Biphenylene)bis[2-hydroxy-4-(2-bromoethyl)-morpholine] dihydrobromide



The request is for 10 g of this target structure. The synthetic sequence, shown in Chart No. 8, is essentially that reported in the literature (9). After some minor modifications in the experimental procedure, a small scale probe synthesis was carried out successfully to intermediate 4. On scale-up, however, the conversion of compound 3 to compound 4 by the exact literature procedure gave a product which was contaminated with 15-20% of the corresponding N-chloroethyl compound. Due to the nearly identical physical characteristics of these two products, purification of the impure compound 4 proved to be impossible. As a result, the synthesis sequence will have to be repeated (in progress). The conversion of compound 3 to compound 4 will be suitably modified to prevent the formation of the chloroethyl impurity.

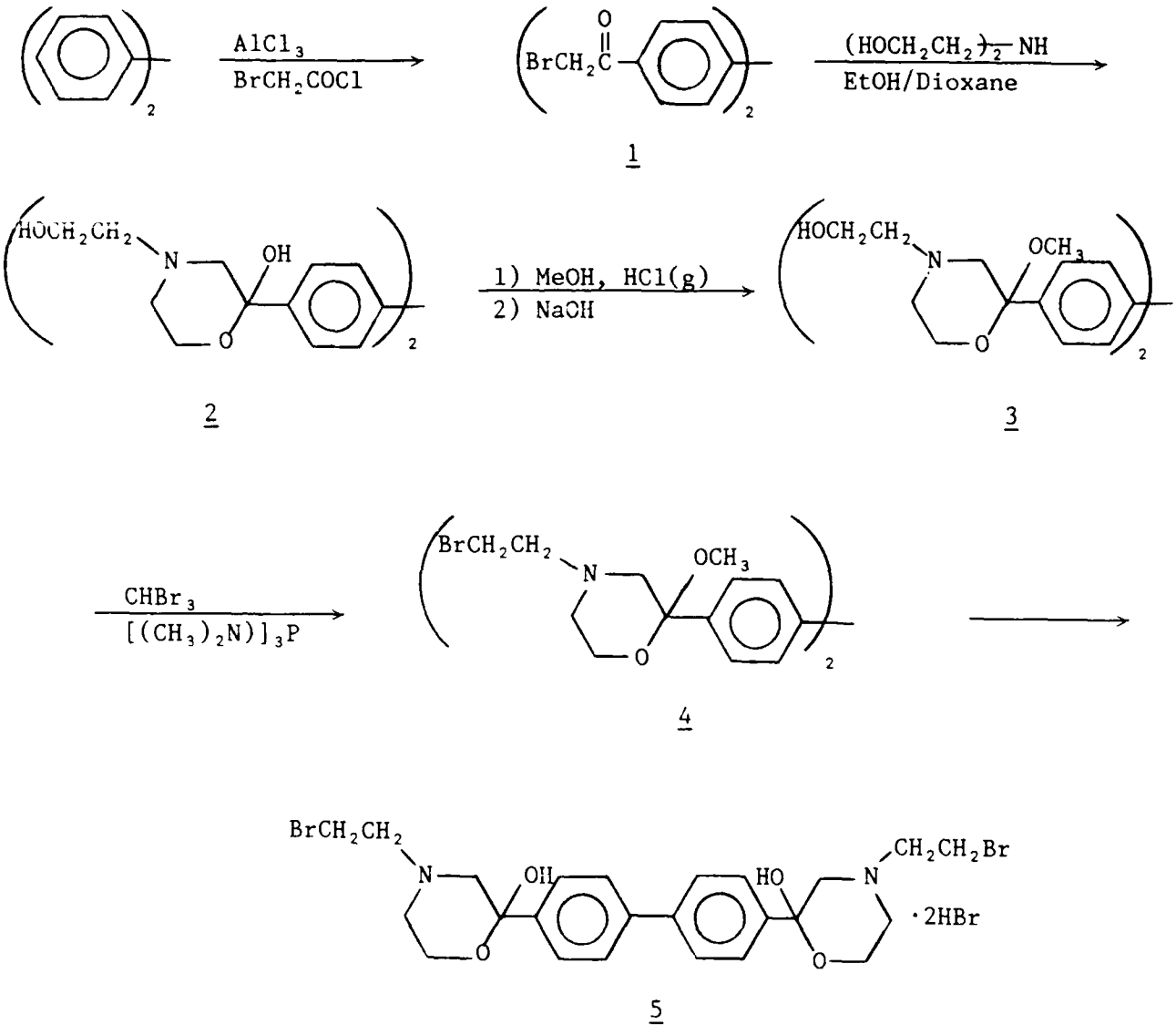
3.2 4-Nitrophenyl 3-phenyl-3-oxopropanesulfonate



The title compound represents a new structure not reported in the chemical literature. A considerable effort was made to synthesize this sulfonic acid ester. Thus, the coupling of benzene with β-bromopropionyl chloride in the Friedel and Crafts reaction gave β-bromopropiophenone. Treatment of this material with sodium sulfite followed by passage of the mixture over a Dowex 50 ion exchange resin led to the isolation of 3-phenyl-3-oxopropanesulfonic acid, a crystalline solid containing 2 mol of water of crystallization. The initial attempts to prepare a 4-nitrophenyl ester involved the coupling of the acid with p-nitrophenol in the presence of dicyclohexylcarbodiimide. Although we have successfully prepared esters of phosphinic acids by this method, we were not able to isolate a product

CHART NO. 8

2,2'-(4,4'-BIPHENYLENE)BIS[2-HYDROXY-4-(2-BROMOETHYL)-MORPHOLINE] DIHYDROBROMIDE



1 2 3 4 5

that could be identified as the title sulfonic acid ester. As an alternate approach the sulfonic acid was treated with phosphorus pentachloride to give a low melting solid, the presumed sulfonyl chloride. This material was not thoroughly characterized but was treated directly with 4-nitrophenol and triethylamine. A crystalline product was isolated in low yield and identified as 3-(4-nitrophenoxy)-1-phenyl-1-propanone. This product is most likely formed by a base-catalyzed elimination of the sulfonyl group to give phenyl vinyl ketone followed by addition of 4-nitrophenol to the carbon-carbon double bond. The same product was prepared in 58% yield by the reaction of β-bromopropiophenone with 4-nitrophenol and triethylamine.

In view of the poor results and the lack of a more promising alternative route, work on this target was suspended.

4. EXPERIMENTAL PROCEDURES

All melting points and boiling points are uncorrected. Infrared spectra were recorded using a Perkin-Elmer 273B spectrometer. Elemental analyses were performed by Midwest Microlab, Ltd., Indianapolis, IN. Vapor phase chromatography was performed using an F and M Model 810 with a flame ionization detector. NMR spectra, when required, were determined on a Varian Model T60 spectrometer. All thin layer chromatography (TLC) was carried out using Analtech Uniplate silica gel GF 250u plates with fluorescent indicator unless stated otherwise.

4.1 4-Nitrophenyl 2-furyl(methyl)phosphinate

The synthesis route to the title compound is shown in Chart No. 1.

Tris(2-furyl)phosphine (1) - Furan (408 g, 6.00 mol) in dry ether (1715 mL) was treated with n-butyl lithium (2.5M, 1708 mL, 4.27 mol) added dropwise over a 2-h period. The mixture was cooled (0°C) and a solution of phosphorus trichloride (82 mL, 0.94 mol) in benzene (854 mL) was added over a 1-h period. After standing at ambient temperature for 18 h, a 10% aqueous ammonium chloride solution (1700 mL) was added carefully. The organic phase was separated, dried ($MgSO_4$), and concentrated (aspirator) to give a crude solid, 182.5 g. This material was distilled to give 153.5 g (70%) of pure compound 1, bp 145°C/0.7 mmHg, as a colorless oil which solidified upon standing, mp 59-61°C; lit. bp 112°C/0.3 mmHg, mp 60-63°C (3).

Tris(2-furyl)methylphosphonium iodide (2) - Methyl iodide 189 g, 1.33 mol) was added to a solution of tris(2-furyl)phosphine (152.7 g, 0.66 mol) in dry benzene (765 mL). The reaction mixture was heated at reflux for 4 days. The reaction mixture was cooled and the precipitated solid was collected by filtration to give 239 g (97%) of pure compound 2, mp 112-114°C, as white crystals; lit mp 112-113°C (3).

Bis(2-furyl)methylphosphine oxide (3) - An aqueous sodium hydroxide solution (2 N, 380 mL, 0.76 mol) was added over 20 min to a solution of tris(2-furyl)methylphosphonium iodide (239 g, 0.64 mol) in water (508 mL) and ethanol (765 mL). The reaction mixture was stirred at ambient temperature for 30 min and then concentrated (aspirator) to one-half of the original volume. This solution was extracted with chloroform (2x380 mL). The combined extracts were dried ($MgSO_4$), charcoaled, filtered, and concentrated (aspirator) to give 105 g of crude phosphine oxide 3, mp 77-79°C. The crude product was crystallized from a mixture tetrahydrofuran (265 mL) and ether (132 mL) to give 83 g (66%) of pure phosphine oxide 3, mp 78-80°C, as a white solid; lit. mp 79-81°C (3).

2-Furyl(methyl)phosphinic acid (4) - A mixture of bis(2-furyl)methylphosphine oxide (82.5 g, 0.42 mol), water (841 mL), and sodium hydroxide (33.7 mL, 0.84 mol) was heated at 90°C for 13 h. The aqueous solution was washed with chloroform (3x75 mL) and taken to pH 1 with concentrated hydrochloric acid (ca. 80 mL). The aqueous solution was concentrated (aspirator) to a paste and the paste was slurried in chloroform (180 mL). The mixture was filtered and the filtrate was concentrated to give 50 g (82%) of crude phosphinic acid 4, mp 68-70°C, as a yellow solid. The crude product was crystallized from a mixture of tetrahydrofuran (76 mL) and ether (80 mL) to give 36 g (58%) of pure phosphinic acid 4, mp 70-72°C, as white crystals; lit. mp 70-72°C (3).

4-Nitrophenyl 2-furyl(methyl)phosphinate (5) - A solution of 2-furyl(methyl)phosphinic acid (36 g, 0.25 mol), 4-nitrophenol (3.33 g, 0.24 mol), and dicyclohexylcarbodiimide (53.4 g, 0.26 mol) in ethyl acetate (180 mL) was heated at reflux for 1 h, cooled and filtered. The filtrate was concentrated (aspirator) to give 41 g of crude phosphinate as a light pink solid. The crude product was crystallized from tetrahydrofuran (45 mL) and ether (90 mL) and gave 34 g (53%) of pure title compound, mp 104-106°C, as a white powder; lit. mp 105-106°C (3)

Anal. Calcd. for $C_{11}H_{10}NO_5P$ (267.17): C, 49.45; H, 3.77; N, 5.24, P, 11.59. Found: C, 49.58, H, 3.97, N, 5.19, P, 11.37.

Thin Layer Chromatography

Eluent	Rf	Comment
Ether	0.35	Homogeneous

4.2 3-Hydroxy-1-methylpyridinium bromide

Methyl bromide (38 g, 0.4 mol) was bubbled into a cold (-10°C) solution of 3-hydroxypyridine (15 g, 0.16 mol) in a mixture of dry acetone (142 mL) and anhydrous ethanol (44 mL). The flask was stoppered tightly and allowed to stand at ambient temperature for 48 h. The precipitated product was collected by filtration, washed with an acetone/ethanol mixture (3:1, 50 mL), and air-dried to give 22.6 g of crude product, mp 138-142°C, as an off-white powder. The crude product was crystallized from a mixture of anhydrous ethanol (74 mL) and ether (150 mL) and gave 19.3 g (64%) of pure title compound, mp 153-155°C (6).

Anal. Calcd. for C_6H_8BrNO (190.04): C, 37.92; H, 4.24; Br, 42.05; N, 7.37. Found: C, 38.04; H, 4.43; Br, 41.81; N, 7.52.

Thin Layer Chromatography

Eluent	Rf	Comment
Chloroform/methanol (9:1)	0.11	Homogeneous

4.3 4-Nitrophenyl dimethylphosphinate

The two step synthesis sequence to the title compound is shown in Chart No. 2.

Dimethylphosphinic acid (1) - To a refluxing slurry of tetramethyldiphosphine disulfide (68 g, 0.37 mol) in carbon tetrachloride (232 mL) was carefully added dropwise a 30% hydrogen peroxide solution (108 mL, 1.05 mol) over a 2-h period. The mixture was refluxed for 1.5-h and allowed to stand overnight at ambient temperature. Precipitated elemental sulfur was removed by filtration. The aqueous layer of the two-phase filtrate was separated and concentrated (aspirator) to a thick oil which was dried at ambient temperature/0.05 mmHg to give 62.6 g, of crude phosphinic acid 1 as a white solid. The crude product was crystallized from a mixture of tetrahydrofuran (355 mL) and ether (60 mL) to give 55.4 g (81%) of pure phosphinic acid 1, mp 88-90°C, as a white crystalline solid; lit. mp 86-89°C (3).

4-Nitrophenyl dimethylphosphinate (2) - To a solution of dimethylphosphinic acid (30 g, 0.32 mol) and 4-nitrophenol (43 g, 0.31 mol) in ethyl acetate (240 mL) was added dicyclohexylcarbodiimide (69 g, 0.34 mol). The reaction mixture was heated at reflux for 1 h and then stirred an additional 2 h at ambient temperature and filtered. The filtrate was concentrated (aspirator) to give 60 g of crude productas a light yellow solid. The crude product was crystallized twice from a mixture of ethyl acetate (250 mL) and ether (250 mL) and gave 22 g (33%) of pure title compound, mp 97-99°C, as a white solid; lit. mp 99-100°C (3).

Anal. Calcd. for $C_8H_{10}O_4NP$ (215.14): C, 44.66; H, 4.68, N, 6.51; P, 14.39. Found: C, 44.48; H, 4.61; N, 6.34; P, 14.56.

Thin Layer Chromatography

Eluent	Rf	Comment
Chloroform/methanol/acetic acid (55:5:4)	0.54	Homogeneous

4.4 4-Nitrophenyl chloromethyl(2-methoxyphenyl)phosphinate

The synthesis route to the title compound is shown in Chart No. 3.

Tetraethylphosphorodiamidous chloride (1) - To a 12 L flask containing a mixture of phosphorous trichloride (300 g, 2.18 mol) and dry petroleum ether (4 L) at -60°C was added dropwise with vigorous stirring a solution of diethylamine (639 g, 8.74 mol) in dry petroleum ether (875 mL) over a 2-h period. The cooling bath was removed and the reaction mixture was allowed to warm to 25°C and filtered to remove precipated salts. The filtrate was concentrated by simple distillation (1 atm, N_2) to give 403 g of crude product as a yellow oil. The oil was distilled to give 372 g (81%) of pure compound 1, bp 58-60°C/0.1 mmHg, as a colorless oil; lit. bp 50-52°C/0.17 mmHg (3); bp 87-90°C/2 mmHg (10).

P-(2-Methoxyphenyl)-N,N,N',N'-tetraethylphosphonous diamide (2) - A 3 L flask was charged with magnesium turnings (26 g, 1.1 mol) and dry ether (85 mL). A solution of 2-bromoanisole (156 g, 0.83 mol) in ether (750 mL) was added dropwise over a 2-h period. When the formation of the Grignard reagent was complete, additional ether (350 mL) was added, and the reaction mixture was cooled to -56°C. Tetraethylphosphorodiamidous chloride (160 g, 0.76 mol) was added neat over a 30-min period. The reaction mixture was allowed to warm to 25°C over a 1 h period with stirring and the salts were removed by filtration. The fitrate was concentrated (1 atm, N_2) to give a yellow oil. The oil was distilled to give 138 g (64%) of pure compound 2, bp 125-127°C/0.45 mmHg, as a colorless oil; lit. bp 115-120°C/ 0.65 mmHg (3).

2-Methoxyphenylphosphonous dichloride (3) - A 2 L flask was charged with ether (500 mL) and dry hydrogen chloride gas (73 g, 2.0 mol) and cooled to -60°C. A solution of P-(2-methoxyphenyl)-N,N,N',N'-tetraethylphosphonous diamide (137 g, 0.49 mol) in ether (150 mL) was added dropwise with stirring over 1 h. The reaction mixture was allowed to stand for 60 h at 20°C and then filtered. The filtrate was concentrated (1 atm, N_2) to a yellow oil. The oil was distilled to give 76 g (74%) of pure compound 3, bp 96-98°C/0.5 mmHg lit. bp 89-93°C/0.7 mmHg (3).

Chloromethyl(2-methoxyphenyl)phosphinic chloride (4) - 2-Methoxyphenylphosphonous dichloride (23 g, 0.11 mol) and paraformaldehyde (4.85 g, 0.17 mol) were added to a 50-mL flask. After stirring for 5 min, a vigorous exothermic reaction occurred. The reaction mixture was then heated at 130°C for 1.5 h. Distillation of the reaction mixture gave 14 g (54%) of the phosphinic chloride 4, bp 110-190°C/0.7-0.3 mmHg, as a thick colorless oil which solidified upon standing. In a similar manner, 51 g of 2-methoxyphenylphos-

phinous dichloride was converted in two batches, to the phosphinic dichloride 4, 31 g (52%). The material from the three runs was combined and used as such in the next step.

4-Nitrophenyl chloromethyl(2-methoxyphenyl)phosphinate (5) - A mixture of 4-nitrophenol (44 g, 0.18 mol), tetrahydrofuran (218 mL), and diisopropylethylamine (35 mL, 0.20 mol) was cooled to 5°C. A solution of chloromethyl(2-methoxyphenyl)phosphinic dichloride (44 g, 0.18 mol) in tetrahydrofuran (157 mL) was added over a 10-min period. The reaction mixture was stirred at ambient temperature for 2 h, filtered, and the solid was washed with tetrahydrofuran (250 mL). The combined filtrate was concentrated (aspirator) to a pale yellow oil. The oil was redissolved in chloroform (450 mL), and the chloroform solution was washed with 1 N HCl (250 mL), 5% aqueous $NaHCO_3$ (250 mL), dried ($MgSO_4$), and concentrated (aspirator) to give an oil which solidified upon standing. The solid was recrystallized from ethyl acetate (150 mL x 2) to give 106 g (17%) of pure title compound, mp 114-116°C, as a white solid; lit. mp 114-115°C, (3).

Anal. Calcd for $C_{14}H_{13}ClNO_5P$ (341.68): C, 49.21; H, 3.83; Cl, 10.38; N, 4.10; P, 9.07. Found: C, 49.20; H, 3.93; Cl, 10.23; N, 4.23; P, 9.19.

Thin Layer Chromatography

Eluent	Rf	Comment
Ether	0.47	Homogeneous

4.5 3-Nitrophenyl 2-propyl chloromethylphosphonate

The synthesis route to the title compound is shown in Chart No. 4.

Bis(3-nitrophenyl) chloromethylphosphonate (1) - A mixture of 3-nitrophenol (250 g, 1.797 mol) and triethylamine (290 mL, 2.081 mol) in tetrahydrofuran (2.5 L) was cooled to 0°C. A solution of chloromethylphosphonic dichloride (158.3 g, 0.946 mol) in tetrahydrofuran (160 mL) was added dropwise over a 1-h period. The mixture was heated at reflux for 1 h and stirred an additional 30 min at ambient temperature. The slurry was filtered, the solid was washed with tetrahydrofuran (1 L) and the combined filtrate was concentrated to a thick oil (321.6 g) which solidified on standing. Recrystallization from ether (23 mL/g) gave pure title compound, 285.9 g (85%), mp 55-57°C.

An earlier, small scale probe reaction gave the same product with an identical melting point. A sample of this material was submitted for elemental analysis.

Anal. Calcd for $C_{13}H_{10}ClN_2O_7P$ (372.66): C, 41.90; H, 2.70; Cl, 9.51; N, 7.52; P, 8.31. Found: C, 41.85; H, 2.86; Cl, 9.36; N, 7.71; P, 8.58.

3-Nitrophenyl chloromethylphosphonic acid (2) - A solution of bis(3-nitrophenyl) chloromethylphosphonate (90 g, 0.2415 mol) in acetonitrile (1350 mL) was cooled to 0°C. Aqueous NaOH (0.5 N, 530 mL) was added dropwise over an 8-h period while maintaining the temperature below 5°C and the pH at 10 or less. After the addition was completed the mixture was adjusted to pH 7 with acetic acid and allowed to stand at ambient temperature overnight. The acetonitrile was removed under reduced pressure (aspirator). The residual solution was diluted with water (500 mL), adjusted to pH 5 with acetic acid and washed with ether (1 L x 5) to remove 3-nitrophenol. The solution was adjusted to pH 1 with concentrated HCl and concentrated to dryness (vacuum pump). The residual white solid was slurried in ethyl acetate (600 mL), the slurry was filtered, and the filtrate concentrated to dryness to give crude product. Recrystallization from ethyl acetate yielded pure acid 2, 30.5 g (50%), mp 114-116°C.

The analytical sample was prepared from an earlier small scale probe reaction and melted at 115-117°C.

Anal. Calcd for $C_7H_7ClNO_5P$ (251.56): C, 33.42; H, 2.80; Cl, 14.09; N, 5.57; P, 12.31. Found: C, 33.29; H, 2.70; Cl, 13.99; N, 5.75; P, 12.32.

3-Nitrophenyl 2-propyl chloromethylphosphonate (3) - A mixture of 3-nitrophenyl chloromethylphosphonic acid (30 g, 0.119 mol), isopropanol (27.4 mL, 0.358 mol) and tetrahydrofuran (180 mL) was cooled to 10°C. A solution of N,N'-dicyclohexylcarbodiimide (DCC), (36.9 g, 0.179 mol) in tetrahydrofuran (60 mL) was added dropwise over a 20-min period while maintaining the temperature below 20°C. After the addition was completed, the mixture was stirred at ca. 20°C for 1 h. Analysis by TLC showed some unreacted 2 present. More DCC (2.7 g, 0.013 mol) was added, the mixture was stirred for 25 min and filtered (celite). The filtrate was treated with aqueous. HCl (0.1 N, 2 mL) stirred for 30 min, refiltered through celite and concentrated to a semisolid mass (50.1 g). This material was chromatographed over silica gel (500 g) eluting with 1:1 ether/hexane to give 31.5 g of product contaminated with some dicyclohexylurea. The compound was dissolved in ether (250 mL), the solution was treated with charcoal (1.6 g), dried ($MgSO_4$), and filtered through celite. The filtrate was concentrated to dryness to give 30.5 g of a yellow solid. Two recrystallizations from ether/petroleum ether gave 16.4 g (47%) of

pure product, mp 41-43°C; NMR ($CDCl_3$) δ 1.37 (d,3H,J=6Hz,CH_3) 1.45 (d,3H,J=6Hz,CH_3) 3.75 (d,2H,J=10Hz,CH_2) 4.95 (m,1H,CH) 7.47-7.77 (m,2H,ArH) 7.9-8.2 (m,2H,ArH).

Anal. Calcd for $C_{10}H_{13}ClNO_5P$ (293.65): C, 40.90; H, 4.46; Cl, 12.07; N, 4.77; P, 10.55. Found: C, 40.70; H, 4.46; Cl, 12.05; N, 4.87; P, 10.75.

Thin Layer Chromatography

Eluent	Rf	Comment
Ether	0.45	Homogeneous

4.6 (3R,6R)-3,6-Dihydroxytropane 3-(S)(-)-tropate hydrobromide

The synthesis sequence to the title compound is shown in Chart No. 5.

(3R,6R) and (3S,6S)-3,6-Dihydroxytropane 3-(S)(-)-tropate (1 and 2) - A solution of scopolamine hydrobromide trihydrate (20 g, 46 mmol) in water (100 mL) was hydrogenated in a Parr apparatus over neutral Raney-Ni catalyst (26.4 g) at 35 psi. After 24 h, the reaction mixture was filtered. This procedure was repeated five times. The combined filtrates were acidified to about pH 5 with concentrated hydrobromic acid and concentrated (bath temperature below 40°C) to about 150 mL. The solution was cooled (ice bath), adjusted to pH 10 with aqueous sodium hydroxide and extracted with chloroform (9 x 200 mL, 4 x 100 mL). The first four extracts contained predominantly an impurity and were discarded. The last nine fractions were combined and concentrated to give the title compound free base, a foamy solid (64.3 g).

In a similar manner, an additional 340 g of scopolamine hydrobromide trihydrate was processed to yield 142 g of foam. This material was used as such in the next step.

(3R,6R)-3,6-Dihydroxytropane 3-(S)(-)-tropate, dibenzoyl-L-tartrate salt (3) - The mixture of compounds 1 and 2 (64.3 g, 0.2 M) was dissolved in ethanol (350 mL) and treated with a solution of L-dibenzoyltartaric acid monohydrate (38.1 g, 0.1 M) in ethanol (230 mL). The resulting solution was stored in a refrigerator for 18 h and filtered to give crude tartrate salt (43.6 g), mp 143-149°C.

In the same manner, an additional 142 g of the mixture was converted to 105.4 g of crude tartrate salt. The combined product (149 g) was recrystallized seven times from a mixture of ethanol (10 mL/g) and water (0.6 mL/g) to give pure title compound (77.4 g), white crystals, mp 160-162°C, $[\alpha]_D^{25}$ -47.2° (c = 1, MeOH); lit. mp 163°C, $[\alpha]_D$ -44° (c = 1, MeOH), (7).

(3R,6R)-3,6-Dihydroxytropane 3-(S)(-)-tropate hydrobromide (4) - A solution of compound 3 (77.2 g, 0.08 mol) in water (500 mL) was eluted through a column of Dowex 2-X8 (bromide form) ion exchange resin (1.8 L, 2.16 mol). The eluate (2.3 L) was concentrated to give a thick clear oil which was azeotroped with absolute ethanol (4 x 400 mL) to give a white powder (56 g). The solid was dissolved in MeOH (150 mL). The solution was diluted with acetone (700 mL), then concentrated to 250 mL and stored in a refrigerator for 18-h. The solid was collected by filtration and recrystallized twice more in this manner to give pure product (35.2 g), white fine crystals, mp 174-175°C, $[\alpha]_D^{25}$ -10.3° (c = 1, H_2O); lit. mp 156°C, $[\alpha]_D$ -10.5° (c = 2, H_2O), (7). ^1H NMR (CD_3OD) δ 1.50-2.60 (m,6H), 3.01 (s,3H), 3.15-4.80 (m,6H), 5.05 (m,1H), 7.40 (s,5H).

Anal. Calcd for $C_{17}H_{24}BrNO_4$ (386.29): C, 52.86; H, 6.26; Br, 20.69; N, 3.63. Found: C, 52.62; H, 6.01; Br, 20.53; N, 3.45.

Thin Layer Chromatography

Eluent	Rf	Comment
Chloroform/methanol/29.4% ammonium hydroxide (8:2:0.2)	0.27	Homogeneous

4.7 4-Nitrophenyl dibutylphosphinate

The synthesis sequence to the title compound is shown in Chart No. 6.

Dibutylphosphinic acid (1) - Diethyl phosphite (66.8 g, 0.48 mol) was added over 1.5 h to a cold (15°C), vigorously stirred ethereal solution of 1-butylmagnesium chloride (590 mL, 1.47 mol). The mixture was refluxed for 3.5 h, and then stirred at ambient temperature overnight. The slurry was poured into ice water (250 mL), acidified to pH 1 with concentrated hydrochloric acid (150 mL), and the residual ether was removed by warming the mixture. Bromine (27 mL, 0.53 mol) was added and the mixture was stirred for 30 min. The solution was extracted with chloroform (2 x 1 L), the combined organic extract was washed with sodium thiosulfate, dried ($MgSO_4$), and concentrated (aspirator) to give 79.2 g of crude dibutylphosphinic acid, mp 49-53°C.

The crude acid was dissolved in ether (500 mL) and treated with dicyclohexylamine (88.5 mL, 0.44 mol). The mixture was stirred in an ice bath for 30 min and filtered to give 124 g of the dicyclohexylamine salt of dibutylphosphinic acid, mp 118-120°C. The salt was dissolved in water (600 mL) and sodium hydroxide pellets (15.2 g, 0.38 mol) were added. The aqueous solution was washed with chloroform (300 mL), the pH was adjusted to 1 with concentrated hydrochloric acid and the solution was extracted with chloroform (2 x 800 mL). The chloroform extract was dried ($MgSO_4$) and concentrated to give a solid which was recrystallized from 50% aqueous methanol (300 mL) to give 41.7 g (65%) of pure product, mp 67-69°C.

Dibutylphosphinic chloride (2) - Phosphorous pentachloride (22.2 g, 0.11 mol) was added to a solution of dibutylphosphinic acid (19 g, 0.11 mol) in dry benzene (183 mL). The reaction mixture was heated at reflux for 2 h, cooled and concentrated (aspirator) to give 21.7 g of a red oil. This material was distilled to give 19.6 g (93%) of the acid chloride, a colorless oil, bp 90°C/0.6 mmHg; lit. bp 163-166°C/22 mmHg, (8).

4-Nitrophenyl dibutylphosphinate (3) - A mixture of 4-nitrophenol (13.4 g, 0.097 mol) and triethylamine (14.8 mL, 0.106 mol) in methylene chloride (180 mL) was stirred at room temperature until a homogeneous yellow solution formed. A solution of dibutylphosphinic chloride (19 g, 0.097 mol) in methylene chloride (20 mL) was added dropwise over a 10-min period. The reaction mixture was heated at reflux for 45 min, cooled, washed with cold 1 N hydrochloric acid (90 mL), cold saturated sodium bicarbonate solution (90 mL) and cold water (2 x 90 mL). The organic phase was dried ($MgSO_4$) and concentrated (aspirator) to a yellow oil which was purified by column chromatography (acidic alumina, 2 x 300 g), eluting with 1:1 methylene chloride hexane. The product-containing fractions were combined, dried ($MgSO_4$), and concentrated (aspirator) to a yellow oil. This material was dissolved in ether, the solution was treated with charcoal, filtered through celite, and concentrated (aspirator) to give 18.8 g (65%) of pure title compound as a yellow oil.

Anal. Calcd for $C_{14}H_{22}NO_4P$ (299.31): C, 56.18; H, 7.41; N, 4.68; P, 10.35. Found: C, 55.99; H, 7.65; N, 4.57; P, 10.33.

Thin Layer Chromatography

Eluent	Rf	Comment
Ether	0.44	Homogeneous

4.8 1,2,3,3a,8,8a-Hexahydro-1,3a,8-trimethylpyrollo[2,3-b]indol-5-ol (7-carboxy)heptanoate ester

The synthesis sequence to the title compound is shown in Chart No. 7.

Eseroline (1) - A solution of physostigmine (11.9 g, 43.2 mmol) in concentrated hydrochloric acid (75 mL) was heated on a steam bath for 45 min. The mixture was concentrated (aspirator, then 0.1 mmHg) to a colorless thick oil. The oil was dissolved in nitrogen-flushed methanol (200 mL) and the solution was reconcentrated (x 2). A solution of aqueous sodium bicarbonate was flushed with carbon dioxide and added to the oil. The mixture was continuously extracted with nitrogen-purged ether for 72 h. The ether extracts were dried ($MgSO_4$) and concentrated (aspirator) to give 9.2 g of crude eseroline as a

white solid. The crude product was recrystallized from nitrogen-purged benzene and hexanes to give 8.1 g (85%) of eseroline, mp 126-128°C; lit. mp 128°C, (11).

1,2,3,3a,8,8a-Hexahydro-1,3a,8-trimethylpyrollo[2,3-b]indol-5-ol 7-(benzyloxycarbonyl)heptanoate ester (2) - A solution of dicyclohexylcarbodiimide (0.92 g, 7.55 mmol) in dichloromethane (35 mL) was added in one portion to a solution of eseroline (4.5 g, 20.7 mmol) and monobenzyl suberate (see below) (6.3 g, 23.8 mmol) in dichloromethane (35 mL). After 2 h, more dicyclohexylcarbodiimide (1.5 g) was added and the mixture was stirred at ambient temperature for 18 h. The precipitated dicyclohexylurea was removed by filtration and washed with dichloromethane. The combined filtrate and wash was concentrated (aspirator) to give 17.4 g of crude product as an oil. This material was purified by column chromatography on silica gel (260 g) eluting with dichloromethane/tetrahydrofuran (6:1). The product-containing fractions were divided into 2 lots and concentrated (aspirator, then 0.1 mmHg) to give 5.5 g and 2.4 g of partially purified title compound. The 2.4-g lot was purified further by column chromatography (36 g silica gel) eluting with ethyl acetate. The product-containing fractions were concentrated (aspirator followed by 0.2 mmHg) to give 2.0 g of pure title compound as a pale green oil. This material was used as such in the next step.

The monobenzyl suberate used above was prepared in-house by the following procedure.

A solution of benzyl alcohol (10.1 g, 93.4 mmol) and triethylamine (17 mL, 122 mmol) in tetrahydrofuran (60 mL) was added dropwise over a 30-min period to a solution of suberoyl chloride (19.8 g, 93.8 mmol) in tetrahydrofuran (120 mL) while maintaining the temperature at 15-20°C. After stirring for 1 h, water (100 mL) was added and the THF was removed at reduced pressure (aspirator). The aqueous solution that remained was extracted with ether (3 x 150 mL). The combined ether extract was dried ($MgSO_4$) and concentrated (aspirator) to give 23.8 g of crude product as an oily solid. This material was purified by column chromatography (700 g, J.T. Baker silica gel, dichloromethane/methanol, 80:1). The product-containing fractions were concentrated to give 7.0 g (28%) of pure monobenzyl suberate, a low melting waxy solid.

1,2,3,3a,8,8a-Hexahydro-1,3a,8-trimethylpyrollo[2,3-b]indol-5-ol (7-carboxy)heptanoate ester (3) - Palladium black (1.3 g) was added to a solution of intermediate 2 (2.0 g, 4.3 mmol) and 1,4-cyclohexadiene (4.1 mL, 43.3 mmol) in anhydrous ethanol (50 mL). The mixture was stirred at ambient temperature under a nitrogen blanket. When the reaction was complete as evidenced by TLC (15-30 min), the solvent was removed at reduced pressure (0.1 mmHg). The residue was dissolved in benzene and the solution was treated with charcoal and

filtered. The filtrate was concentrated (0.1 mmHg) to give 1.4 g (86%) of pure title compound as a very pale brown gum. ^{1}H NMR 300 MHz (CD_3CN) δ 1.37 (s,3H), 1.37 (m,4H), 1.57 (quint, J=7.2 Hz, 2H), 2.47 (t, J=7.2 Hz, 2H), 2.48 (s,3H), 2.53 (m,2H), 2.77 (ddd, 1H), 2.88 (m,1H), 2.90 (s,3H), 4.22 (s,1H), 6.38 (dd, J=2.7, 6.3 Hz, 1H) 6.72 (dd, J=2.7, 6.3Hz, 1H) 6.73 (apparent t, J=2.7Hz, 1H) 8.70 (brs, 1H).

Anal. Calcd for $C_{21}H_{30}N_2O_4$ (374.80): C, 67.35; H, 8.08; N, 7.48. Calcd with 0.18 mol benzene: C, 68.22; H, 8.43; N, 7.48. Found: C, 68.24; H, 8.11; N, 7.20

Thin Layer Chromatography Sybron/Brinkmann Polygram Sil G/UV

Eluent	Rf	Comment
Tetrahydrofuran	0.32	Homogeneous

4.9 5-Nonanone oxime

Sodium bicarbonate (8.86 g, 0.105 mol) was added to a solution of hydroxylamine hydrochloride (6.35 g, 0.091 mol) in H_2O (25 mL). This solution was added in one portion to a solution of 5-nonanone (10 g, 0.07 mol) in 95% EtOH (100 mL). The mixture was stirred for 30 min and the ethanol was removed at reduced pressure (aspirator). The residual solution was diluted with H_2O (100 mL) and extracted with chloroform (2 x 150 mL). The combined extract was dried ($MgSO_4$) and concentrated (aspirator) to an oil which was distilled twice to give 7.8 g (70%) of pure product, bp 60-62°C/0.03 mmHg.

Anal. Calcd for $C_9H_{19}NO$ (157.255): C, 68.74; H, 12.18; N, 8.91. Found: C, 68.59; H, 12.24; N, 8.85.

Thin Layer Chromatography

Eluent	Rf	Comment
Ether	0.70	Homogeneous

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